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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WANG, CHANG YU	

ART UNIT	PAPER NUMBER
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/560,294	MICHEL ET AL.	
	Examiner	Art Unit	
	CHANG-YU WANG	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 March 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5,7,8 and 54-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5,7,8 and 54-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

RESPONSE TO AMENDMENT

Status of Application/Amendments/claims

1. Applicant's amendment filed 3/16/10 is acknowledged. Claims 2, 4, 6, and 9-53 are cancelled. Claims 58-60 are newly added. Claims 1, 3, 5, 7, 8, 54-57 and newly added claims 58-60 are pending in this application and under examination in this office action.

2. Applicant's arguments filed on 3/16/10 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

Claim Rejections/Objections Withdrawn

3. The rejection of claims 1, 5, 7, 8 and 54-57 under 35 U.S.C. 102 (b) as being anticipated by WO01/88104 (Carpenter. published Nov 22, 2001) as evidenced by Baumann et al. (Physol. Rev. 2001. 81:871-927) is withdrawn in response to Applicant's arguments.

The rejection of claims 1, 3, 5, 7, 8, and 54-57 under 35 U.S.C. 102 (b) as being anticipated by US Patent No. 6562619 (Gearhart et al. issued on May 13, 2003, priority Mar 31, 1998) as evidenced by Baumann et al. (Physol. Rev. 2001. 81:871-927) is withdrawn in response to Applicant's arguments.

The rejection of claims 54 and 57 under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn in response to Applicant's arguments on p. 18-20.

Claim Rejections/Objections Maintained

In view of the amendment filed on 3/16/10, the following rejections are maintained.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 54 and 57 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejection is maintained for the reasons made of record and the reasons set forth below.

On p. 18-19 of the response, Applicant argues that the language of claim 54 is clearly defined in the specification because the specification teaches that "gp130 activator is added to the NS cells... either alone or together....". Applicant's arguments have been fully considered but they are not persuasive.

In response, as previously made of record, the culture medium itself contains a lot of growth agents (more than one) to maintain and promote cell survival. In particular, the culture medium for NS cells described in the specification contains DMEM/F12, heparin, FGF-2, insulin, transferring, putrescine, selenite, progesterone (p. 14 & p. 29) and the differentiation medium contains DMEM/F12 with insulin, transferrin, putrescine, selenite, progesterone (see p. 29). These agents are the growth or differentiation agents. Thus, the culture medium itself recited in claim 54 has already contained more than one growth or differentiation agents. However, the claim itself also recites that the gp130 activator is the only growth or differentiation agent, which is in conflict with the

fact that the culture medium contains more than one growth or differentiation agents. Accordingly, the recitation of "the gp130 activator is the only growth or differentiation agent present in the culture medium encompasses a broad range or limitation (i.e. culture medium itself containing a lot of growth agents) together with a narrow range or limitation that falls within the broad range or limitation (in the same claim), which is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Accordingly, the gp130 activator cannot be the only growth or differentiation agent in the culture medium as recited in claim 54 and thus renders the claim indefinite.

On p. 19 of the response, Applicant argues that the metes and bounds of the definition "large and highly branched" are known as compared to normal oligodendrocytes as taught in the disclosure and in the field. Applicant's arguments have been fully considered but they are not persuasive.

Note that although the meanings of "large" and "highly branched" are known, the term "large and highly branched" and the term "large myelin membrane" in claim 57 is a relative term which renders the claim indefinite. The specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention because the term "large or highly branched" is not defined by the claim. Applicant fails to set forth the metes and bounds of how much branching would be considered as "large and highly branched" or "small and less branched", and what size of the myelin membranes would be

considered "small" or large membranes and thus would be within the definition of "large and highly branched" or "large myelin membranes" as recited in instant claim 57. Since the metes and bounds cannot be determined, it is not clear to a skilled artisan as to what size of oligodendrocytes with myelinating activity would be large and highly branched and would exhibit large myelin membranes. Thus, claim 57 is indefinite.

New Grounds of Rejection Necessitated by the Amendment

The following rejections are new grounds of rejections necessitated by the amendment filed on 3/16/10.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 5, 7, 8 and 54-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 6562619 (Gearhart et al. issued on May 13, 2003, priority Mar 31, 1998, cited previously) in view of Zhang et al. (Nat Biotechnol. 2001, Dec, 1129-1133, as in IDS) as evidenced by Baumann et al. (Physol. Rev. 2001. 81:871-927) and Billon et al. (J. Cell Sci. 2002. 115: 3657-3665, as in IDS).

Claims 1, 3, 5, 7, 8 and 54-60 as amended are drawn to a method of generating $O1^+$ and/or $O4^+$ oligodendrocytes comprising growing neurosphere (NS) cells in a culture medium that promotes differentiation of NS cells into $O1^+$ and/or $O4^+$ oligodendrocytes, said culture medium comprising one or more gp130 activators selected from the group consisting of CNTF, oconstatin-M (OSM) or IL-6, IL6R/IL6 chimera and IL-11 and wherein said culture medium specifically enhances differentiation into O1+ and/or O4+ oligodendrocyte lineage, thereby causing the NS cells to differentiate along the oligodendrocyte lineage into O1+ and/or O4+ oligodendrocyte lineage. Dependent claims 54 and 60 are directed to one or more gp130 activator is the only growth or differentiation agent and dependent claims 56 and 57 are directed to the culture medium promotes myelinating activity and formation of

large and highly branched O+ and/or O4+ oligodendrocytes exhibiting large myelin membranes.

US Patent No. 6562619 (the '619 patent) teaches a method of differentiating oligodendrocytes comprising growing embryonic stem (pPS) cells including mouse and human embryonic stem cells in the presence of a gp130 activator including IL-6 and IL-11 as recited in instant claims (see col. 28, example 6; col. 30, claims 1-28, in particular). The '619 patent teaches that embryonic stem (ES) cells cultured in the standard culture medium form embryoid bodies (see col.. 29, lines 29-40; col.30, claim 9). The '619 patent teaches that embryoid bodies are allowed to replate in insulin-transferin-selenium-fibronectin (ITSN) supplemented medium dissociated and replated into medium containing basic fibroblast growth factor (bFGF) (col. 15, lines 16-col. 16, line9, in particular). The '619 patent teaches that upon removal of FGF, neurons, astrocytes, and oligodendrocytes are expected to form in situ. Further, the '619 patent teaches that the culture medium for differentiation in the method of the '619 patent contains FGF, LIF and IL-6 or IL-11(see col. 28, example 6; col. 30, claims 1-28, col. 14, line 27-col. 15, line 4 in particular). The '619 patent also teach a method of generating oligodendrocytes comprising growing human embryonic stem cells in the presence of a gp130 activator including a oncostatin-M (OSM) or LIF as recited in instant claims (see p. 237, abstract; p. 237, 2nd col.-p. 238, 1st col., in particular). Note that LIF, oncostatin-M (OSM), IL-6 or IL-11 is a gp130 activator as recited in instant claims 1, 3, 54 and 60. But the '619 patent does not teach neurosphere (NS) cells and oligodendrocyte marker O1+ and/or O4+ as in claims 1, 7, 8, 57 and 60.

Although the '619 patent does not explicitly teach neurospheres derived from embryoid bodies, the cells disclosed by the '619 patent are re-suspended and passaged through 1-3 passages (7 to 30 days) (col. 24-25, examples 1-2 and 6, in particular).

Zhang et al. teach that human embryonic stem (ES) cells cultured in a defined medium containing FGF-2 (bFGF) for a week differentiate into O4+, O1+ and GFAP+ neural precursor cells (see p. 1129-1130, in particular). Zhang further teaches that when continuing exposure to FGF-2, the above isolated human ES-derived neural precursor cells can form columar rosette cells (i.e. embryoid bodies). In addition, Zhang teaches that when the above cells were expending as free-floating cell aggregates in a suspension culture, these human ES-derived neurosphere can be maintained up to 8 passages and can be differentiated into neurons and glia in a similar pattern as early passages. Zhang further teaches that upon removal of FGF-2 (bFGF), the above cells can be differentiated into neurons, glia and oligodendrocytes (see p. 1129, in particular). Note that based on the teaching of Zhang, human derived-ES cells can form embryoid bodies and neurospheres in the culture of human ES cells in the presence of FGF-2 as evidenced by Billon et al. (see p. 3658, 2nd Col., 3rd paragraph-p. 3659, 1 st col., 2nd paragraph, in particular, J. Cell Sci. 2002.115: 3657-3665, as in IDS). Thus, the cells through 1-3 passages of re-dissociation, resuspension and repassages from embryoid bodies (i.e. originally derived from embryonic stem cells) taught by the '619 patent would also give rise to neurospheres because the cells cultured in the method of the '619 patent are re-suspended and passaged and cultured in the same manner as the cells in Zhang and as in instant specification (col. 24-25, examples 1-2 and 6, in

particular). Thus, the cells derived from embryoid bodies as taught by the '619 patent would have similar properties as neurospheres recited instant claim 1.

Although the '619 patent does not explicitly teach expression $O4^+$ and $O1^+$ markers on differentiated oligodendrocytes as recited in instant claims 1, 7, 8, 57 and 60, Zhang et al. teach that human embryonic stem (ES) cells cultured in a defined medium containing FGF-2 (bFGF) for a week differentiate into O4+, O1+ and GFAP+ neural precursor cells (see p. 1129-1130, in particular). In addition, the expression of these markers on differentiated oligodendrocytes is an intrinsic feature of differentiated oligodendrocytes as evidenced by Baumann et al. (see p. 875, 2nd col, 2nd -3rd paragraphs, in particular, Physol. Rev. 2001. 81:871-927). Baumann teaches that markers of differentiated oligodendrocytes including O4+ and O1+ (see p. 875, 2nd col, 2nd -3rd paragraphs, in particular).

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to use neurospheres or human ES-derived neurospheres in the method of the '619 patent to generate O1+ and/or O4+ oligodendrocytes in the presence of a gp130 activator such as CNTF, OSM, LIF, IL-6 or IL-11. The person of ordinary skill in the art would have been motivated to do so with an expectation of success because neurospheres can be derived from embryoid bodies from cultured human ES as taught by Zhang and the cells expanded and re-suspended from embryoid bodies that are originally derived from human ES cells in the presence of a gp130 activator such as CNTF, OSM, LIF, IL-6 or IL-11 can be differentiated into O1+ and/or O4+ oligodendrocytes as taught by the '619 patent.

Given the examination guidelines for determining obviousness under 35 U.S.C. 103 in view of the Supreme Court decision in KSR International Co. V. Teleflex Inc. 82 USPQ2d 1385 (2007) and the Examination Guidelines set forth in the Federal Register (Vol. 72, No. 195, October 10, 2007) and incorporated recently into the MPEP (Revision 6, September 2007), the following rationales to support rejection under 35 U.S.C. 103(a) are noted:

A) Combining prior art elements according known methods to yield predictable results.

B) Simple substitution of one known element for another to obtain predictable results.

C) Use of known technique to improve similar products in the same way.

D) Applying known technique to a known product ready for improvement to yield predictable results.

E) "Obvious to try" --- choosing form a finite number of identified, predictable solutions, with a reasonable expectation of success.

F) Some teachings, suggestion, or motivation in the prior art that would lead to one of ordinary skill to modify the prior art reference to arrive at the claimed invention. In this case, the claimed method is obvious over the prior art because the claimed method is by combining prior art elements according known methods to yield predictable results and is a simple substitution of one known element for another to obtain predictable results and. The instant method is to simply replace "the cells derived from embryoid bodies" with "neurospheres" in the method of '619 patent because cells

expanded or derived embyoid bodies would have similar properties derived from neurospheres and cells derived embryoid bodies cultured in a free-floating suspension would give rise to neurospheres. Thus, the results from the claimed are expected. Obviousness is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See KSR International Co. V. Teleflex Inc. 82 USPQ2d 1385 (2007). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Conclusion

6. NO CLAIM IS ALLOWED.

7. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers relating to this application may be submitted to Technology Center 1600, Group 1649 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chang-Yu Wang whose telephone number is (571) 272-4521. The examiner can normally be reached on Monday-Thursday from 8:30 AM to 6:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached at (571) 272-0911.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/CYW/
Chang-Yu Wang, Ph.D.
May 25, 2010

/Christine J Saoud/
Primary Examiner, Art Unit 1647